DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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April 3, 2002

Dr. John R. Sladek, Jr.
Vice Chancellor for Research
Campus Box A095
School of Medicine, Room 1660
Chancellor's Office
University of Colorado
Health Sciences Center
4200 East 9th Avenue
Denver, CO 80262

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1494

Research Project: Prospective, Randomized, Multicenter Trial of 12 ml.kg vs 6 ml/kg Tidal Volume Positive Pressure Ventilation and Ketoconozole vs Placebo for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome
Journal Article: Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome, The Acute Respiratory Distress Syndrome Network, New England Journal of Medicine. 2000; 342(18): 1301-08.
Principal Investigator: Edward Abraham, M.D.
UC Study Number:96-06

Dear Dr. Sladek:

The Office for Human Research Protections (OHRP) has reviewed the University of Colorado Health Sciences Center's (CU's) report dated March 20, 2002, that was submitted in response to OHRP's January 31, 2002 letter regarding the above-referenced research.

Based upon its review, OHRP makes the following determinations regarding CU's oversight of the above-referenced research:

(1) HHS regulations at 45 CFR 46.116(d) require that the Institutional Review Board (IRB) make and document four criteria when waiving the requirements to obtain informed consent. In its January 31, 2002 letter, OHRP found no evidence in the IRB records that the CU IRB made and documented these four criteria when it approved the principal investigator's November 6, 1998 request for a waiver of the requirement to obtain informed consent for collection of data from the medical records of patients who were screened for participation but were not enrolled.

Corrective Action: OHRP finds that CU has taken appropriate corrective action to address this finding. In particular, OHRP acknowledges that the CU IRBs use a primary reviewer system in which the primary reviewer uses a checklist. This checklist includes the criteria necessary to approve research and to waive consent. The CU IRBs also use additional checklists in the review of protocols involving prisoners and children. OHRP notes that the "Special Questions for Research on Fetuses" and "Special Questions for Research Involving Pregnant Women" should be updated to reflect the revised Subpart B (http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm)

(2) In its January 31, 2002 letter, OHRP found that the informed consent documents reviewed and approved by the CU IRB failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116 (a):

> (a) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts.
>
> (b) Section 46.116(a)(8): A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Corrective Action: OHRP finds that CU has taken appropriate corrective action to address this finding. In particular, OHRP acknowledges that the CU IRBs have revised their practices to ensure that all informed consent documents include all the required elements by requiring investigators to undergo informed consent training, including these requirements in "Instructions to Clinical Investigators," and requiring language that complies with 45 CFR 46.116(a)(8).

(3) HHS regulations at 45 CFR 46.116 require that the information provided in the informed consent documents be in language understandable to the subject. OHRP finds that the informed consent document approved by the CU IRB for this study included complex language that would not have been understandable to all subjects or their legally authorized representatives. In particular, OHRP finds that some of the sentences and terminology were too complex (e.g., "Depending on the results of the randomization procedure, either 12 ml/kg or 6 ml/kg of oxygen-enriched air will initially be delivered to your lungs;" "Subsequently, any changes in the volume will be determined by the pressures in your airways and by the acidity of the blood;" and the discussion of risks).

Corrective Action: OHRP finds that CU has taken appropriate corrective action to address this finding. OHRP acknowledges that the CU IRBs have continued to focus efforts on improving the readability of informed consent documents such as assigning non-scientific members to review documents for readability utilizing a checklist, and having high school representatives on the pediatric board who provide valuable feedback on the content of the informed consent documents. In addition, the "Instructions to Clinical Investigators" and investigator training instruct investigators to write informed consent documents at an eighth grade reading level, and the CU IRBs provide consent templates.

(4) OHRP finds that CU has adequately responded to the additional concerns and questions raised in OHRP's January 31, 2002 letter.

As a result of the above determinations, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

At this time, OHRP provides the following guidance:

(5) OHRP notes that on the Reviewer Protocol Checklist, only certain vulnerable populations are listed. OHRP recommends the addition of categories of "economically or educational disadvantaged persons" and "other."

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. James H. Shore, CU
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Dr. Allan Prochazka, Co-Chair Panel B
Dr. Stephen Barlett, Co-Chair Panel B
Dr. Adam Rosenberg, Co-Chair Panel C
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